ACUTE GENERALIZED MILIARY TUBERCULOSIS *

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Since the first description of acute generalized miliary tuberculosis by Bayle [1] (1810) there has been controversy concerning the pathogenesis of this disease. The main question has been whether the generalized dissemination of foci throughout the various organs of the body originated from a softened caseous focus (Buhl [2]), a vascular focus (Weigert [3-7]), or from within the thoracic duct.

A critical review of the literature leaves the impression that the rôle of active extrapulmonary tuberculous processes in the production of the dissemination has been underestimated and too much stress laid upon the search for vascular foci.

This study has been undertaken in order to review my cases of acute generalized miliary tuberculosis and, in the light of advanced knowledge of tuberculosis, to correlate the pathogenesis, pathology and clinical findings.

MATERIAL

In 1656 consecutive autopsies on tuberculous persons, performed in a period of 8½ years, there were 297 cases (17.9 per cent) of acute generalized miliary tuberculosis. One hundred and ninety-one of the 297 cases showed varying degrees of chronic pulmonary tuberculosis in combination with the miliary dissemination; in 106 cases a generalized miliary seeding existed alone. Orth,[8] who found that more than half of his 30 cases of acute generalized miliary tuberculosis were associated with chronic pulmonary tuberculosis, is the only writer with whose findings my own coincide. Beginning with Weigert,[3] all other authors who discussed this relationship indicated their convictions that the presence of chronic pulmonary tuberculosis excludes the development of acute miliary tuberculosis. This "Ausschliessungsverhältnis" that the more extensive the chronic pulmonary tuberculosis the less the chance for the development of an acute miliary tuberculosis, has been accepted by Schmincke,[9] Huebschmann,[10] Liebermeister,[11] Schürhoff,[12] Schürmann,[13] Grethmann [14] and Pagel.[15, 16]

I feel that the discrepancy between these findings and my own, results from the fact that these authors have interpreted the miliary foci found in lungs in conjunction with chronic pulmonary tuberculosis as representing bronchogenic spread from these chronic pulmonary lesions and have interpreted the miliary foci in the other organs as

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terminal hematogenous disseminations from the lungs. I feel that they have failed to recognize the combined picture.

General Considerations

There are a number of striking differences between the group of acute generalized miliary tuberculosis and the one in which this condition is combined with chronic pulmonary tuberculosis.

Age. From Table I it may be seen that in both groups the greatest number of cases is observed in the age period between 20 and 39 years. This does not agree with Grethmann [14] who has reported that youth and the older ages are chiefly involved, with the middle ages relatively free of miliary tuberculosis. Nor does it agree with Huebschmann [10]

Table I
Age Distribution

	Birth to 10 yrs.	11–19	20–29	30–39	40–49	50–59	60–69	Over 70
Acute generalized miliary tuberculosis	21	10	30	26	11	4	4	0
Acute generalized miliary tuberculosis and chronic pulmonary tuberculosis	11	10	46	48	35	30	10	1

and Hartwich [17] who emphasized the preponderance of acute generalized miliary tuberculosis in the first 2 decades. There is an interesting contrast in the early and late age distribution in both groups. There were 31 patients (29.2 per cent) who were less than 20 years of age in the series of uncombined acute generalized miliary tuberculosis and only 19 patients (17.9 per cent) who were older than 40 years. In the cases of acute generalized miliary tuberculosis combined with chronic pulmonary tuberculosis, on the other hand, there were 21 individuals (10.9 per cent) who were less than 20 years of age, whereas 76 (39.8 per cent) were more than 40 years of age.

This interesting contrast may in part be related to the source of the miliary tuberculosis. My studies have revealed that bone tuberculosis occurs chiefly in the younger age groups while the preponderance of male genital and urinary tuberculosis occurs in the older age groups. Bone tuberculosis was found in 48 of the 106 cases of acute generalized miliary tuberculosis; urogenital tuberculosis was found in 114 of the 191 cases of acute miliary tuberculosis combined with chronic pulmonary tuberculosis.

Color. In the 106 cases of uncombined acute generalized miliary tuberculosis 72 (67.9 per cent) were negroes, while 34 (32.1 per cent) were white. One hundred and twenty-two (63.9 per cent) of the 191

individuals showing acute generalized miliary tuberculosis combined with chronic pulmonary tuberculosis were white, while 67 (35.1 per cent) were negro and 2 (1 per cent) were of the yellow race.

Sex. An almost parallel distribution in respect to sex is present in the two groups. In the cases of uncombined acute generalized miliary tuberculosis, 73 (68.9 per cent) were males, while 33 (31.1 per cent) were females. In the other group, 147 (76.9 per cent) were males and 44 (23.1 per cent) were females.

Pathogenesis

Most of the discussion has centered upon the source of the hematogenous dissemination. Laënnec [18] (1810) was the first to point out that older soft caseous foci could lead to extensive dissemination throughout other organs. Buhl,[2] carrying his teachings farther, stated that in the majority of the cases of acute generalized miliary tuberculosis there were older caseous foci in the body. He suggested the resorption of the "specific substance" into the blood stream.

Huguenin [19] who shared Buhl's [2] view believed that the caseous mass could either erode and enter a small vein, or invade the lymphatics.

Weigert,[7] on the other hand, stated that, since this caseous focus is frequently not found, its occasional presence in cases of acute miliary tuberculosis is not sufficient evidence for belief in it as the source of the dissemination. He pointed to the infrequent occurrence of acute generalized miliary tuberculosis in conjunction with well developed phthisis. Since, he reasoned, in phthisis there are caseous processes and softened foci as well, and since these are apparently insufficient for the development of acute miliary tuberculosis, there must be other factors which allow the entry of masses of tubercle bacilli into the blood stream. In 1879 Weigert [6] observed a case of acute generalized miliary tuberculosis wherein a large caseous lymph node extended into the right innominate vein. In subsequent studies he found other venous tubercles in cases of acute generalized miliary tuberculosis. Accordingly, Weigert [3-6] contended that the vascular tubercle progresses from a tuberculous focus, which extends to the vessel's wall and after destroying its intima, ruptures into the blood stream. This focus is often referred to as the "Weigert" tubercle in spite of the fact that in one study he found vascular foci in only 50 per cent of the cases and in another in 70.8 per cent. This view of the vascular focus has been accepted by Pagel,[16, 20] Hartwich,[17] Schmorl,[21] Sigg,[22] Silbergleit,[23] Baar,[24] Dittrich,[25] Herxheimer,[26] Schwarz [27] and Berghammer.[28]

Benda,[29-31] likewise, believed that the vascular focus was responsible for acute generalized miliary tuberculosis. However, he considered that

the ulceration of a solitary metastasis within the intima rather than the erosion of the vessel wall by an extravascular focus was the source of the dissemination.

Ponfick [32] (1877) found that in the majority of his cases of acute generalized miliary tuberculosis he could demonstrate small tubercle-like nodules within the intima of the thoracic duct. It was his opinion that the tubercles in the thoracic duct were the result of the original hematogenous dissemination. Subsequently Schürhoff [12] and Grethmann,[14] in reviewing Ponfick's studies, stated that Ponfick did not recognize the tuberculosis of the thoracic duct as being primary and the generalized tuberculosis as being secondary.

Wild,[33] arguing against the views of Weigert, stated that there are too many cases (30 to 50 per cent) in which a focus cannot be found in the vein or thoracic duct. It was this author's opinion that small numbers of tubercle bacilli enter the blood stream from an active tuberculous process in the body (skeleton, urinary system, or other organ) and that the bacilli multiply in the blood stream due to certain favorable factors such as increasing virulence of the organism and special dispositional factors of the host. Ribbert [34, 35] shared Wild's views.

Huebschmann [10, 36, 37] rejected Weigert's views and stated that it is frequently impossible to isolate the source of the tubercle bacilli despite diligent search. He stipulated two factors leading to the generalization. The mechanical factor of a tubercle bacillus bacteremia (based on the findings of Loewenstein [38] and Liebermeister [39]) may be said to exist in all forms of tuberculosis. The dispositional factor depends upon (a) the specific component or lack of disseminated resistance in the body; and (b) the nonspecific component, or the unrelated metabolic and infectious processes of the host.

In a later study Loeschcke [40] (1931) postulated the development of acute generalized miliary tuberculosis as the result of a direct communication between a caseous focus and the blood stream without intermediate tubercle formation. Such a caseous focus, he pointed out, must contain large numbers of organisms, and through softening and liquefaction bacilli are released into the general circulation. Following this evacuation, blood enters the focus and can be readily detected microscopically. In a study of his cases of acute miliary tuberculosis which developed just before death he found grossly visible bleeding at the site of rupture with great regularity. The caseous focus which ruptured into the blood stream was usually a lymph node, but it was not infrequent to find it in the skeletal system, prostate, testis, or adrenals.

The findings of Loeschcke [40, 42] were subsequently substantiated by Minguez.[41]

A study of my own material does not allow me to accept any of the views of pathogenesis which are based on the assumption of the rupture of a tuberculous focus into the blood stream. It is my opinion that the development of acute generalized miliary tuberculosis is the result of the drainage of tubercle bacilli from an active extrapulmonary tuberculous focus (skeletal system, urogenital system, serous surfaces) or a primary focus (usually progressive) into the lymphatic system. This in turn empties into the venous system (through the well known lymphovenous routes).

It is interesting to note that Buhl [2] and Ponfick [32] alone have stated that the development of a generalized miliary tuberculosis may be the result of lymphatic drainage from a caseous focus.

The presence of an acute tuberculous process in one or more organ systems in every one of my cases of acute generalized miliary tuberculosis contradicts Huebschmann [10] whose observations led him to state that the two only occasionally occur together, and that there was probably an "excluding state" between the two conditions. Pagel [15] and Baar,[24] on the other hand, were not impressed by these "excluding" conditions, while Reisner [43] stated that the opposite seems to be the case.

It has been repeatedly stated that isolated organ-tuberculosis (third stage tuberculosis of Ranke, postprimary tuberculosis), in contrast to primary tuberculosis, is characterized by the absence of gross caseation of the lymph nodes. Although this is observed in the majority of cases of chronic pulmonary tuberculosis, the same may not be said of tuberculous involvement of other organ systems. It has been my repeated observation from autopsy material that progressive tuberculous involvement of the skeletal, urinary and genital systems is almost invariably characterized by caseous tuberculosis of the regional lymph nodes. The regional lymph nodes are also enlarged and caseous when there is a caseous process of the pleura, peritoneum and pericardium, and when there is extensive and deep-seated ulceration of the gastrointestinal tract. Unlike the primary complex the caseous involvement of the regional lymph nodes does not occur at the onset but usually develops in the later stages of the process. The enlargement and caseation of the lymph nodes is often not limited to the regional glands but may involve the neighboring chains.

The lymph node involvement indicates extensive lymphatic drainage of tubercle bacilli from the neighboring organ-tuberculosis, a phenomenon similar to that observed in any infection. This migration of

tubercle bacilli into the lymph nodes has been demonstrated by bacterial stains. The tubercle bacilli are carried in the lymph to the venous circulation and a generalized blood stream dissemination takes place with the development of miliary foci in the various organs of the body. Two important factors must be clarified in the consideration of a dissemination occurring in this manner: (1) caseation of regional lymph nodes does not necessarily mean that a blood stream dissemination will develop in every instance, just as it does not always develop from a pyogenic infection. The caseous process may be, and probably frequently is, walled-off with no resultant hematogenous dissemination. (2) After invasion of the blood stream takes place, the caseous involvement of the lymph nodes may become circumscribed by fibrous tissue. Repetition of the hematogenous dissemination is thus avoided and the hematogenous foci may undergo healing changes. Ample proof of this is seen at autopsy. It was observed most frequently in children in whom the generalization developed secondarily to a primary complex. These patients showed the caseous lymph nodes to contain calcium and to be encircled by a hyalinized connective tissue capsule; the tubercles in the various organs showed evidence of far advanced healing. Death, in these cases, was occasionally the result of tuberculous meningitis which developed from the generalization, but more often this cause was not related to tuberculosis.

Unlike the "Weigert tubercle," vascular perforation, or thoracic duct focus, the caseous lymph node is always present when there is a generalized miliary dissemination. It is difficult to imagine how caseous lymph nodes, laden as they are with tubercle bacilli, could exist without sooner or later pouring their contents into the general circulation via the efferent ducts.

Lymphatic drainage with subsequent hematogenous dissemination is observed in cases of chronic pulmonary tuberculosis (with or without gastrointestinal tuberculosis). The dissemination occurs most frequently into the spleen and kidney (liver is excluded because of possible portal drainage from gastrointestinal tuberculosis), but sometimes also into the adrenals and other organs including the brain. This hematogenous dissemination was observed in 33.2 per cent of the cases showing chronic pulmonary tuberculosis without associated extrapulmonary foci. In most instances caseous foci could be demonstrated within the tracheobronchial lymph nodes only on microscopic examination, but in some, particularly the more acute cases, the lymph nodes were grossly caseous. The hematogenous foci were more numerous and more widely disseminated in the individuals in whom the lymph nodes were grossly caseous.

Further propagation of the hematogenous dissemination occurs through the development of ulcerative tuberculous foci in the pulmonary veins. These foci develop in the walls of the veins (from within or without) in the course of the original seedings in the lungs. They undergo ulceration and the caseous contents laden with tubercle bacilli are carried to the left side of the heart and thence into the greater circulation.

Pathology

General Distribution

A true evaluation of the question of general distribution is beset by a number of difficulties. Whereas the lung readily lends itself to the gross identification of miliary tubercles, other organs are less productive on simple inspection. Easy recognition is of considerable importance, particularly when the dissemination is not extensive, since one millimeter foci may so readily be overlooked in routine examinations. In these instances, successful gross examination would be of immeasurable value. This is best exemplified in the kidney where division into 2 or 3 mm. slices will frequently reveal the presence of miliary tubercles overlooked in the routine examination. Such meticulous examination is of no aid in the heart, adrenals, pancreas, or thyroid gland because in these organs such foci are not recognizable on gross examination. A true incidence therefore, of the distribution within these organs can be ascertained only by serial section, a physically impossible task. The brain was removed for examination in only a small number of cases.

When the dissemination is extensive routine microscopic examination will reveal miliary tubercles in almost all parenchymatous organs.

Miliary foci were found in the lungs and spleen in all instances; in the kidney in 205 cases (69.0 per cent), in the adrenals in 84 cases (28.3 per cent), in the brain in 31 cases (10.4 per cent), in the pancreas in 14 cases (4.7 per cent), and in the thyroid in 10 cases (3.4 per cent).

Lungs

Clinical and Anatomic Correlations. The gross appearance, histologic characteristics and serial roentgenograms must all be considered in determining the development and ultimate fate of the miliary tubercle. Since all of the 297 patients in my series were in our institution, suffering from some form of extrapulmonary tuberculosis, an excellent opportunity was afforded to study the development and ultimate fate of the miliary dissemination. In this correlation only those cases were considered in which the lungs were clear before the hematogenous dissemination. The only proof of pulmonary seeding is the roentgeno-

gram; clinical signs and symptoms must be verified by x-ray examination. Huebschmann and Arnold,[44] in attempting to arrive at a classification of hematogenous seeding based on clinical signs and symptoms, came to the conclusion that there is a definite relationship between the clinical and anatomic pictures of generalized miliary tuberculosis; this, in spite of the fact that a number of their clinical observations did not coincide with the anatomic findings. Grethmann [14] and Pagel [15] emphasized the difficulty of correlating the age of the disease with the clinical data. None of the authors mentioned roentgenographic studies as correlation. I feel that this is a vital omission.

Some of the patients in my series whose earlier roentgenograms showed either clear fields or at most a few scattered foci in the apical portions, and who were observed over a period of months, developed diffuse disseminations in the lungs. Yet gross and microscopic studies revealed both recent and very old foci. The answer to this discrepancy lies in the fact that sufficiently early roentgenographic observations were not available. Occasionally, however, I have had the opportunity of observing the following course: a patient with some form of extrapulmonary tuberculosis has a roentgenogram which clearly demonstrates a diffuse miliary lung field dissemination. Subsequent studies then demonstrate progressive clearing from the caudal toward the apical aspects until, finally, no foci are visible or, at most, they are limited to the superior portions of the upper lobe. After a number of weeks or months another dissemination is observed and if the patient lives long enough another clearing may occur from below upward. Microscopic studies explain the apparent disappearance of the foci in the roentgenograms. One of the cases in my series had four separate seedings in the course of 15 months. These were demonstrated by x-ray and confirmed by microscopic examination which clearly demonstrated miliary lesions of four separate age groups. If this patient had been admitted to the hospital after the third dissemination had cleared roentgenologically, one would have had the mistaken impression that death had occurred after one seeding and that the foci were all of a recent date.

Not all individuals show clearing of the foci; some show progressively increasing numbers of miliary foci in subsequent roentgenograms —evidence of further disseminations. It has been my experience from serial roentgenographic studies, and from gross and microscopic examinations, that with the exception of those patients who die shortly after their first disseminations, the hematogenous seedings are usually multiple.

Gross Appearance, Distribution and Size. The dissemination in the

lungs is present from the apices to the bases. The foci are larger and more numerous in the apical parts and become smaller and less numerous toward the caudal aspect. They are larger and more numerous in the anterior than in posterior aspects of the individual lobes. Although most of the foci throughout the lung are approximately 1 mm. in size, those in the apico-ventral aspect of the upper lobe may measure 2 to 3 mm. and often have the appearance of acinous foci. Those in the posterior and basal portions of the lower lobes are almost invariably less than 1 mm. in size.

This variation in size and distribution has been variously interpreted by a number of authors. Buhl [2] and Ribbert [35] believed that miliary tuberculosis begins in the apices and progresses toward the bases so that the larger tubercles are the older ones and the smaller are the younger. Roentgenographic studies reveal the fallacy of this view. When dissemination occurs it is diffuse throughout the lung parenchyma. Schmorl [21] attributed the difference in size to factors which are more favorable for the rapid growth of tubercles in the upper parts of the upper lobe.

The answer to this question may lie in the posture of the lungs. Medlar and Sasano [45] injected tubercle bacilli intravenously into rabbits and strapped one group in an upright position for 10 hours daily and kept the other group in the normal position. They found that in the latter animals the tuberculous process developed chiefly in the posterior parts of the lung while those in the upright position had a preponderance of the lesions in the anterior areas. In both positions the lesions developed chiefly in the apical portions.

In a recent study [46] I pointed out the effect of mechanical compression of the lungs (thoracoplasty, artificial pneumothorax, empyema) on the dissemination of foci within the parenchyma. When dissemination occurred in these cases the noncompressed lungs contained the typical miliary seedings; the compressed lung showed none, or a markedly decreased number. Similar is the distribution of foci within lung parenchyma when chronic pulmonary tuberculosis precedes the seedings. The extent of this dissemination depends upon the amount of uninvolved lung parenchyma present before the hematogenous seeding occurs. The miliary foci appear in the previously clear lung tissue and the extent varies from the presence of seedings in all lobes to a distribution of foci limited to the lower part of one or both lower lobes. Foci in the upper lobes are larger than those in the lower lobes.

The most recent dissemination in my series was observed 5 days before death and the oldest dissemination occurred 15 months prior to autopsy examination. Thus the opportunity has been afforded to study

generalized miliary tuberculosis in all stages of development. Only for a limited period after the first dissemination do all the foci appear to be of the same age. In a short time they are of varying anatomic ages because of repeated seedings.

The foci in the earlier stages of development are yellow in appearance and fuse irregularly with a surrounding lung parenchyma which is firm and red. Although some of the tubercles are round or oval, most of them are irregular. In the later stages of development the tubercles are spherical, gray and well demarcated from a surrounding lung parenchyma which is resilient and often emphysematous. These foci represent the older seedings and are smaller than those in the earlier stages. Also usually present throughout the lung parenchyma are yellow foci (more recent disseminations).

Some of the cases in my series afforded the opportunity of studying far-advanced healing. The foci were either invisible to the naked eye or appeared as small gray or gray-black strands of tissue surrounded by emphysematous lung tissue. They were present chiefly in the apical portions of the upper lobes.

Microscopic Appearance. There has been much discussion as to whether the tubercles develop within the alveolar spaces (intra-alveolar) or in the interstitial tissue (interalveolar). My own findings substantiate the former contention. The first change is that of an alveolar filling process composed of polymorphonuclear leukocytes, alveolar phagocytes, occasional red blood cells and variable amounts of fibrin. In many instances fibrin is entirely absent. The alveoli thus involved are from two to five in number. A few of the surrounding alveoli contain alveolar phagocytes, lymphocytes and occasional red blood cells. The capillaries in the interstitial tissue here are dilated and filled with blood; this is the perifocal reaction.

As the process continues the area of pneumonia may either (1) undergo caseation or (2) be invaded by productive elements. (1) In the first instance the exudate within the alveoli and the fixed tissue elements undergo caseation and with the hematoxylin and eosin stain the focus has a pink-blue granular, and later a pink, appearance. The elastica and van Gieson's stain reveals that the elastic fibers of the alveolar septa, blood vessels and bronchioles within the zone of caseation are still intact. Surrounding the area of caseation is a zone of fibroblasts, epithelioid cells, giant cells and collagen fibrils. I have noted that exudate containing fibrin has a greater tendency to undergo caseation. (2) In this case fibroblasts, epithelioid cells, giant cells and collagen fibrils invade the focus. In the earlier stages the alveolar structure is well retained and the productive elements are intermingled

with the exudative components in the alveolar spaces and are present within the walls of the alveolar septa. As the process continues these productive elements within the alveoli replace the exudate and destroy the septal walls. The end result is an oval or round tubercle in which the underlying lung architecture is completely destroyed.

Healing is observed within the miliary tubercles in both types of foci. The peripherally placed productive elements of a focus with a central zone of caseation extend into this caseous center and gradually replace it. As the process continues, the collagen fibrils formed by the epithelioid cells and fibroblasts increase in number and fuse. With this progression a concomitant decrease in the cellular elements results until finally only a concentric zone of hyalinized connective tissue remains. A focus of the cellular type, in its progression to healing, shows an increase and fusion of the collagen fibers with again a disappearance of the cellular elements with the final formation of a concentric zone of hyalinized connective tissue. Subsequently these areas of connective tissue lose their concentric arrangement, become flattened and, with the disappearance of the specific elements, the resultant scars cannot be differentiated from those caused by other inflammatory processes.

As these cellular foci are transformed into hyaline connective tissue they gradually decrease in size. The surrounding alveolar septa which are intimately adherent to them become stretched and, as the tubercles become smaller, tear. This results in alveolar dilatation and even bleb formation around the healing and healed tubercles. The hyperventilation of the areas encircling these healing tubercles and the diminution in the size of the foci themselves cause a partial or complete disappearance of the characteristic x-ray picture of miliary seeding. Since the foci in the basal areas are smaller and less numerous, the fading of the foci from the roentgenogram is noted first in this portion. As healing progresses there is a progressive "resolution" toward the apical region, and if the source of the hematogenous dissemination has been shut off, all the foci disappear permanently from the roentgenogram. The foci, on gross examination, are visible to the naked eye for a long time after they have disappeared from the x-ray field. Very often, however, a new dissemination appears before the previous seeding has completely "resolved" roentgenographically.

Spleen

Gross. With the exception of those cases in which the dissemination is extensive, miliary tubercles are not distinguishable from splenic corpuscles. When perceptible, they appear as gray elevated nodules which stand out above the cut surface as fine granules. They are approxi-

mately 1 mm. in size and in some regions there are larger foci which have a yellow appearance. I cannot agree with Huebschmann [10] that only the inexperienced cannot distinguish tubercles from the splenic corpuscles, the follicles being gray and the tubercles white.

Microscopic Examination. Although sometimes seen in the splenic corpuscles, tuberculous foci are usually present in the splenic pulp. This is in contrast to the findings of Gråberg,[47] Heitzmann [48] and Lubarsch [49] who found tubercles predominantly in the follicles. My observations as to the development of the tubercle agree with those of Huebschmann and Arnold,[44] Baumgarten,[50] and Schleussing.[51] The earliest changes observed were those of tissue damage. (Tubercle bacilli are numerous and easily demonstrated in the paraffin section at this stage.) This tissue damage is characterized by focal areas of necrosis in which numerous nuclear remnants give the area a blue, granular appearance with the hematoxylin and eosin stain. The underlying splenic architecture is still discernible within the focus in this stage of development. Polymorphonuclear leukocytes are always present and sometimes, in addition, there are occasional epithelioid cells. The question arises as to whether the stage of primary tissue damage is followed by an exudative phase characterized by the presence of polymorphonuclear leukocytes and fibrin and followed in turn by the productive reaction, or whether it is followed directly by the productive reaction. The difficulty in answering this question lies in the fact that most of the foci when first seen are too far advanced to make discriminating observations.

I tend to agree with Huebschmann [10] who felt that the exudative reaction (polymorphonuclear leukocytes and sometimes fibrin) may either go on to caseation or be followed directly by the invasion of the productive elements. If caseation should develop it is encircled by a narrow zone of epithelioid cells, fibroblasts with occasional collagen fibrils and giant cells. Within the caseated area in the earlier stages nuclear remnants and occasional polymorphonuclear leukocytes are present, an indication that the stage of caseation follows the exudative phase. More frequently have I observed the direct invasion and replacement of the exudative elements by the productive components. The result is the formation of an epithelioid-giant cell tubercle which is oval or round. With the invasion of the productive elements the underlying architecture is rendered indiscernible. Thus the spleen in the fully developed stage is studded with oval and round epithelioid-giant cell tubercles, some of the foci containing central regions of caseation. I have not been convinced that caseation ever follows the productive stage.

Healing of the tubercles occurs under the same circumstances and in the same manner as in the lungs. With the complete hyalinization of the foci all signs of specificity disappear and the origin of the connective tissue cannot be determined.

Kidney

In a generalized miliary dissemination one would expect to find miliary tubercles in 100 per cent of the cases. I believe that the reason why 34.1 per cent of cases are negative lies in the technical difficulty in thoroughly examining the kidneys for tubercles. The negative cases include those in which healing of miliary foci was found in other organs and those in which miliary dissemination was not extensive in the spleen or lungs. I think that my search was sufficiently complete to determine definitely the absence of foci. A thorough search would necessitate sectioning the kidney into 2 or 3 mm. slices, followed by serial microscopic study if no foci were found by such detailed gross examination.

Gross. In cases of diffuse generalized dissemination numerous foci are visible on the surface of the kidney when the capsule is removed. These foci appear as flat yellow areas, usually from 1 to 2 mm. in size, which fuse irregularly with the surrounding renal parenchyma. In the earlier stages a narrow red zone surrounds the miliary tubercles. Upon the cut surface the foci are frequently seen as linear areas which lie parallel to the radial rays. They are most frequent in the corticomedullary region, less common in the cortex and least numerous in the medulla.

Microscopic Appearance. The development and ultimate fate of the tubercle is similar to that in the spleen.

Adrenal Gland

Although the adrenal glands showed tuberculous involvement in 98 cases, 84 (28.2 per cent) actually contained miliary tubercles. The other cases presented large caseous foci which often caused marked enlargement of the gland. The anatomic picture of these latter foci clearly indicated that their development preceded the miliary dissemination into the other organs. In a number of cases such nodular caseous tuberculosis was limited to one side, and the miliary involvement of the opposite adrenal was similar to that seen in the spleen and kidneys.

Gross. Miliary tubercles are rarely visible in the adrenal gland on gross examination. When they can be seen, they appear as relatively few gray or gray-yellow foci present mainly in the cortex.

Microscopic Appearance. The appearance of miliary tubercles of the adrenal is similar to those of the spleen and kidney. They are most frequently found in the zona fascicularis of the cortex and are usually not numerous.

Conclusions

As a result of a pathologic analysis of 297 cases of acute generalized miliary tuberculosis, a revised concept of the pathogenesis of the condition is presented for consideration. The invariable presence of caseous lymph nodes in these cases and the analogous situation to that in other infectious diseases lead to the conclusion that the lymphovenous circulation provides the mechanism for miliary dissemination.

The correlation of several roentgenographs with the anatomic appearance of the miliary foci in each patient demonstrated that a hematogenous dissemination of tubercle bacilli sufficient to produce generalized miliary foci is not necessarily an incurable condition. Such correlation demonstrates the almost invariable occurrence of multiple seedings, some or all of which may resolve.

The usual concept, that the concomitant presence of chronic pulmonary tuberculosis and acute generalized miliary tuberculosis is very rare, is not confirmed by this study. This combination occurred in 64.3 per cent of the cases in the series upon which this paper is based.

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